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Local vaccine production

Issues of quality and viability

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Contents

Abbreviations

BCG	Bacille Calmette-Guérin, vaccine against tuberculosis
CVI	Children's Vaccine Initiative
DTP	diphtheria-tetanus-pertussis vaccine
GMP	Good Manufacturing Practice
GNP	Gross National Product
NRA	National Regulatory Authority
OPV	oral polio vaccine
SWOT	strengths, weaknesses, threats, opportunities
TT	tetanus toxoid
UNICEF	United Nations Children's Fund
WHO	World Health Organization

Abstract

A large proportion (measured in terms of doses) of the traditional vaccines used in the national immunization programmes of developing countries are produced domestically (local production).[1]

In 1992, as part of the activities of the Task Force on Situation Analysis of the Children's Vaccine Initiative (CVI), World Health Organization (WHO) staff[2] began a study of the characteristics of local vaccine production in developing countries under the auspices of CVI. Since that time, CVI has carried out thirteen full-scale vaccine supply assessments and over thirty smaller assessments in developing nations around the world.

The survey revealed numerous problems with the quality, cost and reliability of the vaccines produced by these manufacturers as well as the manufacturers' inability to effectively manage epidemiological, organizational and technological changes. The survey also pointed to a set of factors that appear to be necessary for long term viability. These factors should enable governments and donors to maximise the returns of their technological and financial support by focusing it on the producers that are most likely to be successful. As the study demonstrates, local production is a viable option only for meeting a developing country's vaccine needs when it is well supported both politically and financially. However, the potential disadvantages of relying on local manufacturers are significant, and must be carefully understood and addressed in order to ensure a reliable stream of high quality vaccines.

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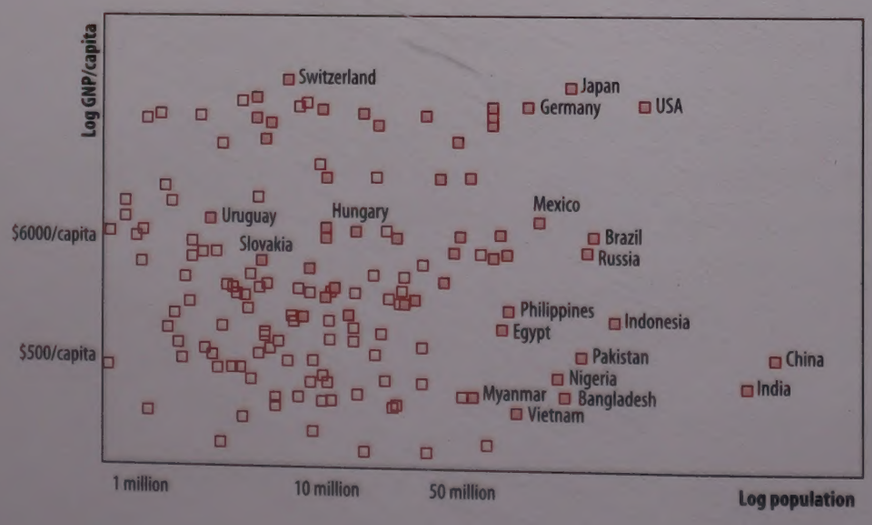
[1] The "traditional" vaccines are defined as those against polio, diphtheria, tetanus, pertussis, measles, tuberculosis and hepatitis B.

[2] These WHO staff are currently based in the Vaccines and other Biologicals Department of the Health Technology and Pharmaceuticals cluster.

Introduction

Domestic (hereafter "local") vaccine production is widespread throughout the world and constitutes the major source of vaccines used in national immunization programmes. As such, local production has been, and continues to be, part of the success of global immunization initiatives. An estimate prepared in 1993 indicated that more than 60% of doses of vaccines used in developing countries are locally produced.[3] A look at the countries which are producing vaccines (Figure 1) shows that almost all larger countries and many mid-sized countries produce vaccines.[4] For mid-sized countries, while neither GNP per capita nor population determines the likelihood of

Figure 1. The extent of local vaccine production. Countries are arrayed as a function of size (x-axis) and relative wealth (GNP/Capita, y-axis). Countries with vaccine production facilities are shaded.



[3] Milstien, J.B., Evans, P., Batson, A. Discussion: Vaccine production and supply in developing countries. 1994. *Vaccination & World Health*, eds Cutts and Smith, John Wiley, pp 60-66.

[4] Larger countries are those with populations greater than 50 million, while mid-sized countries are those with populations between 10 and 50 million.

local vaccine manufacture when considered in isolation, these two factors, when taken together, do correlate strongly with the existence of local production.

In 1992, as part of the activities of the Task Force on Situation Analysis of the Children's Vaccine Initiative (CVI), World Health Organization (WHO) staff[2] began a study of the characteristics of local vaccine production in developing countries under the auspices of CVI. Since that time, CVI has carried out thirteen full-scale vaccine supply assessments and over thirty smaller assessments in developing nations around the world.

This paper will attempt to set forth the characteristics of local producers that most closely relate to long term viability. The hope is that this project will enable donors and governments to evaluate local production with the care and scrutiny necessary to ensure a safe, efficient and cost effective supply of vaccines for developing nations.

Current situation

The studies that formed the basis for this paper assessed local producers in developing countries in four separate areas: (1) the quality of their product, (2) the reliability of their production process, (3) the cost and price of the vaccines they produced and (4) their ability to assess and manage the changes brought about by new technologies and products.

Quality

The quality of a vaccine is generally expressed in terms of its safety, efficacy, and purity. While many locally-produced vaccines meet international quality standards in each of these areas, there are numerous examples of products that fail one or more of these standards, some of which are given below:

- One of the manufacturers examined by CVI produced meningitis vaccine. When a routine quality control test noted a higher than usual rate of reported adverse reactions associated with the use of a particular lot, the National Regulatory Authority (NRA) investigated the situation further. They discovered that while the laboratory tests performed by the manufacturer for that lot met the specifications approved in the licence, the lot was notably different from other lots produced by the manufacturer. Good Manufacturing Practice (GMP) guidelines,[5] as propagated by the WHO, dictates that such lots should be discarded. The NRA had not been aware of the discrepancy in this lot, however, and it had been released and subsequently caused widespread adverse reactions.
- Another country had produced tetanus toxoid vaccine for many years. However, a case-control study in one district disclosed a lower than expected vaccine efficacy, that is, a higher than expected rate of cases of neonatal tetanus in infants born to immunized women. Subsequent testing of the vaccine revealed that the potency was well below the minimum level suggested by WHO guidelines.[6] No National Regulatory Authority existed in the

[5] World Health Organization, Technical Report Series 822 (1992), Annex 1.

[6] World Health Organization, Technical Report Series 800 (1990), Annex 2.

country to ensure that the potency tests used by the manufacturer were properly standardised and validated. The vaccines produced by this manufacturer were a hazard both to vaccinees and their infants and to the credibility of the immunization programme.

- In several countries, lot testing of BCG vaccines produced by local manufacturers has occasionally shown evidence of bacterial contamination. Lot testing is a final product test to ensure that the vaccine itself is pure and contains no other strains of bacteria which could interfere with efficacy or safety. In one case, although there was no National Regulatory Authority, the vaccine manufacturer eventually stopped production until the problem could be resolved.

In all the above cases, vaccines did not meet international quality specifications because the relevant National Regulatory Authorities' or manufacturers' testing and production standards were not high enough. Many countries have not developed the infrastructure needed to ensure the vigorous and independent oversight needed to ensure the safety and efficacy of locally produced vaccines.

WHO has defined six essential control functions which should be carried out by an independent and competent National Regulatory Authority for all countries producing vaccines.[7] These functions are designed to ensure the safety and efficacy of each lot of vaccine produced and to guarantee the consistency of production in an inherently variable biological production system. However, for 52 vaccine-producing countries where these national control functions have been inventoried, 18 of them have not provided for the exercise of all six functions. In addition, the examples above show that even when the functions exist in a given country, they may be carried out ineffectively.

Problems in vaccine quality can have a major negative impact on national immunization programmes. Unsafe or ineffective vaccine threaten to destroy vaccine delivery systems that might otherwise prevent the deaths of millions of infants and children each year.

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[7] *Licensing in accordance with written requirements, post-marketing surveillance for field performance, lot release, laboratory testing, inspections for compliance with Good Manufacturing Practice, review of clinical data*, World Health Organization, Technical Report Series 822 (1992), Annex 2.

Reliability

The second characteristic examined in the study was the reliability of local vaccine production. Local producers were assessed for their ability to meet national demand in a reliable, timely fashion, and for their ability to use donations of equipment and technical advice (a factor which can dramatically impact their ability to remain consistent suppliers over time in the face of changing technology). Several examples were found of inefficient practices in both of these areas.

Table 1 gives an indication of the ability of four typical local production facilities to meet national demand for the product(s) they produce.[8] As the table indicates, these local producers are all far from meeting 100% of their respective national demands. This means that the countries which use these suppliers must obtain vaccines from at least two sources. Increasing the number of suppliers can increase training expenditures as workers are taught to handle different packaging. More importantly, using local suppliers with low volume production subjects a country to greater uncertainty in vaccine supply. In some cases, the failure of a single lot may mean the difference between a programme's ability to immunize children, and having to close down until another source of vaccines can be found.

Table 1. Percentage of national demand by vaccine met by selected local producers

Country	Vaccine	% National needs met
A	OPV from bulk	4
	Measles	37
B	TT	24
C	BCG	71
	OPV from bulk	83
	DTP	9
D	DTP	22
	TT	100

Many countries have received donations of equipment and technical support to improve vaccine production. Under the current system, this support is often either wasted, or used in a highly inefficient manner. Reports of teams fielded by CVI in 13 countries indicate that much of

[a] All four of the facilities used in this example underwent extensive analysis through CVI missions.

the costly equipment donated to local producers stood unused, while some of it had never even been unpacked.[9] Human resources donated to local producers are also frequently wasted because the local staff cannot implement the consultant's advice due to budget constraints and lack of authority. The same is true of international training courses: the workers who receive the training often find that they can get a job which pays more than the vaccine manufacturer and leave shortly after their training is completed: effectively converting an international donation. The end result is that, even if a manufacturer wants to increase production, and has the support of outside donors and agencies, it will frequently be unable to meet domestic needs.

In short, the small scale of local vaccine production, and the inability of concerned donors to increase it, creates a situation in which the national supply of critical vaccines must often be supplemented from outside sources. This multiplicity of sources has many negative consequences, and undercuts much of the rationale for investing in local production in the first place.

Cost

Many developing countries have traditionally believed that producing vaccines locally would be less expensive than importing them because of lower domestic labour costs and the ability to avoid hard currency expenditures. Recent analysis has not been kind to this theory. WHO and UNICEF commissioned Mercer Management to perform a study of the economics of vaccine production. This study showed that vaccine production is dominated by fixed costs, and becomes less labour intensive as technologies evolve. As such, vaccine production is extremely sensitive to economies of scale, with larger production volumes always resulting in lower per-dose production costs.

Moreover, in industrialised countries, vaccine producers offer tiered prices: charging more in developed countries allows the manufacture to sell at lower prices in the developing world. Because first-world markets are not available to developing country producers, they cannot use the high margins these markets provide to cover cost, putting them at even more of a competitive disadvantage with international producers.

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[9] The thirteen countries are: Bangladesh, Brazil, Egypt, India, Indonesia, Iran, Mexico, Nigeria, Pakistan, Philippines, Senegal, South Africa and Thailand. Copies of the CVI reports for these countries are available on request.

Financial assessments of vaccine production facilities in developing countries have shown that the true costs of production are often hidden. For example, donated buildings and equipment may not be included in the calculations of per-dose production costs, and staff costs may come from a different budget. In addition, it is usually true that vaccine production depends on the use of items which can only be bought with hard currency – production media, fermentation equipment, filling lines, vials (Table 2). In fact, for many facilities in developing countries, the largest proportion of costs is related to the import of hard currency-requiring raw material. Because, as mentioned above, vaccine production is a relatively capital and equipment intensive enterprise, facilities making small numbers of doses have a relative high cost per dose. These fixed cost expenditures almost always more than offset the savings that come from a less expensive domestic labour supply. Thus, when true costs are

Table 2. Vaccine production costs in less-developed countries

Cost element	LDC (vs DC)	Notes
Labour	Lower	Labour usually less than 5% of vaccine average cost
Raw materials	Higher	Often imported from DCs
Capital	Higher	Typical loans carry 20%+ rate of interest
Equipment	Higher	Often imported from DCs and subject to duties
Facilities	Somewhat lower	Construction costs are low, but achieving GMP standards can be challenging
Regulatory costs	Lower	In part due to weak NCAs leading to lower costs at risk of compromised product quality

Source: Futures Group Study Pakistan, 1997

calculated, locally produced vaccines are frequently far more expensive than those purchased in the global market. For example, in Indonesia, because of expensive investment in new facilities for the production of OPV and measles vaccines, and the concomitant high maintenance and running costs for these facilities, the manufacturer requested and received from the government an agreement to raise the prices of these vaccines above the global market price.

A second consideration is that some countries with local vaccine production pay twice for vaccines. Governments often pay a flat rate to the production facility regardless of the actual yield of product which can be supplied to the national immunization programme. Yet, as noted above, many of these countries are not meeting national needs, and thus the country must import vaccines to carry out their immunization goals, effectively paying twice for the vaccines they use.

Finally, even if local producers charge the government less than the international market rate, their price may be artificial in that it does not actually cover the costs of production or of maintaining reliable, quality local production. Such essential expenditures as these may not be adequately reflected in estimates of the total costs of local production. Also, as is often seen, investment in maintenance or training may be dropped and the facility gradually runs down. Table 3 shows representative data found by the CVI teams in 1993.

Thus, on the cost side, local production may not save the government money, and in fact may be more expensive. Moreover, to keep vaccine prices at an affordable level, the production facility may be forced to make choices which dictate against future ability to produce vaccines and endanger quality: investment and staff development may be lost in cost saving measures.

Table 3. Actual cost and price data for local production facilities (arbitrary units)

Country A

Facility	Total revenues	Total costs	Total net
Facility 1 (DTP)	4.4	7.8	-3.4
Facility 2 (BCG)	1.4	3.3	-1.9

Country B (1 facility)

Vaccine	Price per dose	Unit cost	Net per dose
Measles	0.02	0.11	-0.09
DTP	0.02	0.04	-0.02
OPV	0.01	0.02	-0.01

Ability to manage change

If the picture is grim for local production of existing vaccines, most of which are made by technologies that are 30 to 50 years old, it is worse when production of new products is considered. Based on direct assessment of a number of local production facilities, seven key factors can be identified which predict a manufacturer's ability to handle change and be viable in the long term.[10]

- Economies of scale
- Consistency of production/GMP
- Access to new technologies
- Historical ability to meet national needs
- Credibility of quality
- Management structure
- Legal status

Figure 2 is a graphical representation of the relationship between the above mentioned factors, needed capital investment and the future viability of local, public-sector vaccine manufactures in the developing world. The graph was generated by assigning a value to each of the indicators mentioned above. When a manufacturer did not have adequate capability in a given area, the authors estimated the amount of investment that would be required to remedy the deficiency. The sums of the scores for the seven categories and the amount of additional investment required were summed independently for each producer, and plotted on the axes of the graph below.

Figure 2 is instructive in that it allows a rational prioritisation of external support to vaccine production activities. Those facilities in the "viable" category are, for the most part, capable of becoming consistent and reliable vaccine producers and need limited but focused technical support. On the other hand, support to the 11 facilities characterised as having a "low probability of viability" is likely to be inefficient and to have little impact unless it is at a very high level and coordinated with strong government commitment.

The "low probability" facilities share a number of characteristics which impact their future survival: (1) they tend to produce only one or two

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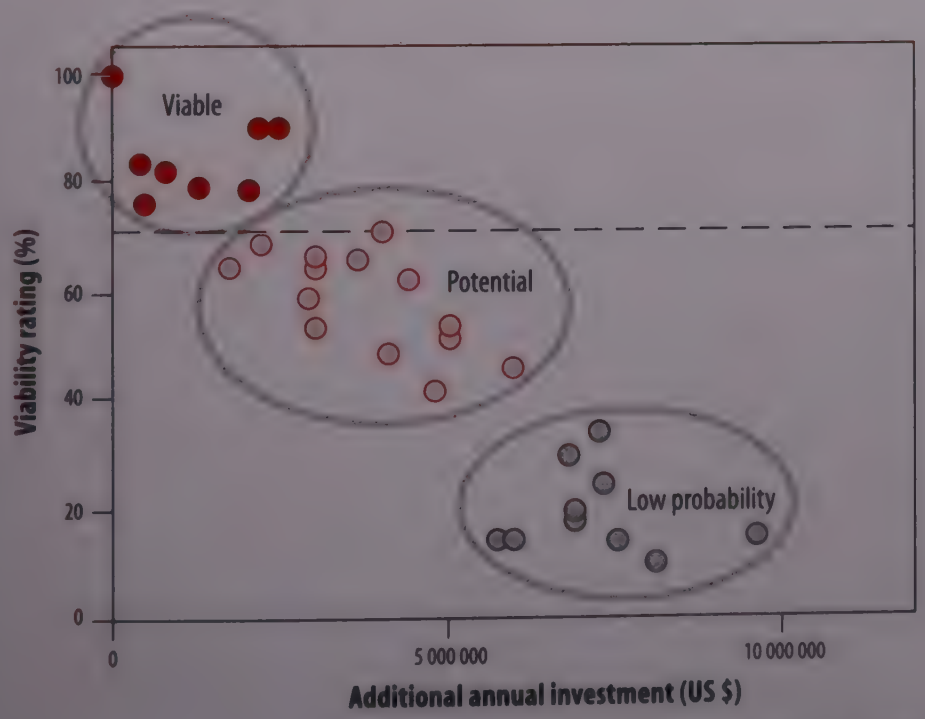
[10] J. Milstien, A. Batson, W. Meaney. A systematic method for evaluating the potential viability of local vaccine producers, *Vaccine*, 15:1358-1363, 1997.

vaccine products, (2) are able to provide only a fraction of national needs for these products (3) several of their products have been associated with reports of poor quality (4) none of them are located in a country with a fully functional National Regulatory Authority, and (5) none of the facilities has a viable research and development unit, nor a visible strategy for accessing new vaccines and technologies. A decision on the part of donors and governments to cease support to these facilities would likely result in their dissolution. International funds could better be used to promote the development and strengthening of national control functions in these countries in order to improve the quality and reliability of vaccine supply in the long term.

Appropriate support to the facilities in the largest category, the "potentially viable" facilities, can have a large positive impact on the future of local vaccine production. As a group, the single largest impediment to viability for these facilities is the legal structure and autonomy with which they are allowed to operate: that is, their ability to set salaries, control the recruitment of staff, revenues and budgets, and to ensure stability for these functions in the face of changing political climates. Additional impediments are related to access to new technologies and appropriate management structures, including

Figure 2. The viability of local vaccine production.
The graph shows three distinct groupings of public sector developing country vaccine manufacturers: those which are viable, those which are potentially viable, and those with a low probability of attaining viability.



Source: V&B/ATT, 02/99

marketing departments and budgets for product and process development and staff training. While these facilities are generally overseen by National Regulatory Authorities, the NRAs in question could, in most cases, benefit from technical support. Furthermore, none of the studied facilities belonging to this intermediate group has undergone a critical assessment of their problems to allow the development of a strategic plan for future activities. A decision on the part of donors and governments to cease support to "potentially viable" facilities would likely have a large impact on national vaccine supply, as they are generally supplying significant amounts of most, if not all, antigens to their domestic immunization programmes. However, focused support for long term strategic planning and strengthening national control infrastructures could result in large dividends for global vaccine supply, especially for new vaccines.

CASE STUDY

A successful local vaccine producer [11]

Perum Bio Farma, located in Bandung, Indonesia, is a state-owned company, solely responsible for the production of vaccines for human use in Indonesia. Founded in 1890, it has had the formal status of a Perum – a public enterprise – since 1978. In 1988, the current President Director was brought in from the private sector, because Bio Farma had been classed as an "unhealthy" Perum. They produced at that time BCG and the DTP group of vaccines in old facilities. The new management initiated a SWOT (strengths, weaknesses, opportunities, and threats) analysis and set new priorities, including the production of measles and polio vaccines, long-term planning, production capacity, marketing, human resources, and research and development.

The management team then set out to achieve the goals they had set for themselves. The measles and polio vaccine project was completed with Japanese assistance.[12] A new agreement to produce hepatitis B vaccine for the Indonesian immunization programme was concluded with an international producer, production capacity was increased to meet national needs, and production processes were upgraded to meet Good Manufacturing Practice. By 1993, Bio Farma was classified a "healthy" Perum. Today, it has become a Persero (limited company) with more of the characteristics of a private sector facility. Moreover, its excellence in production technology, compliance with Good Manufacturing Practice, and the functioning of the Indonesian National Regulatory Authority have been recognized by the inclusion of Bio Farma on the list of prequalified suppliers for measles and polio vaccines to UN agencies.

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[11] Taken from a presentation by Dr Djoharsjah, Finance and General Affairs Director, Perum Bio Farma, entitled, "A case in management of public sector vaccine manufacturer," at a WHO Workshop on Management of Local Production of Vaccines, New Delhi, 22–26 May, 1995

[12] This assistance involved significant financial and technical investment from the donor government over a seven-year period.

SUMMARY

The future of public sector production

Table 4 summarises some of the pros and cons of public governance of vaccine production. Although it is clear that local production can be responsive to national vaccine needs and viable in the long term, it will only do so where there is focused assistance and attention to the elements listed in previous sections. Governments and potential donors intending to support local production must understand the ways in which these characteristics affect viability, and develop the capacity to determine when it is efficient and profitable to aid a facility. If these factors are not considered before support is given, the locally produced vaccine supply could, at best, be irrelevant to national vaccine needs. At worst, there could be a double standard in vaccine quality, with recipients of locally produced vaccine receiving low quality – potentially unsafe or ineffective – vaccine, while those who received vaccines purchased from inter-national sources benefiting from much better protection.

Table 4. Public governance of vaccine production

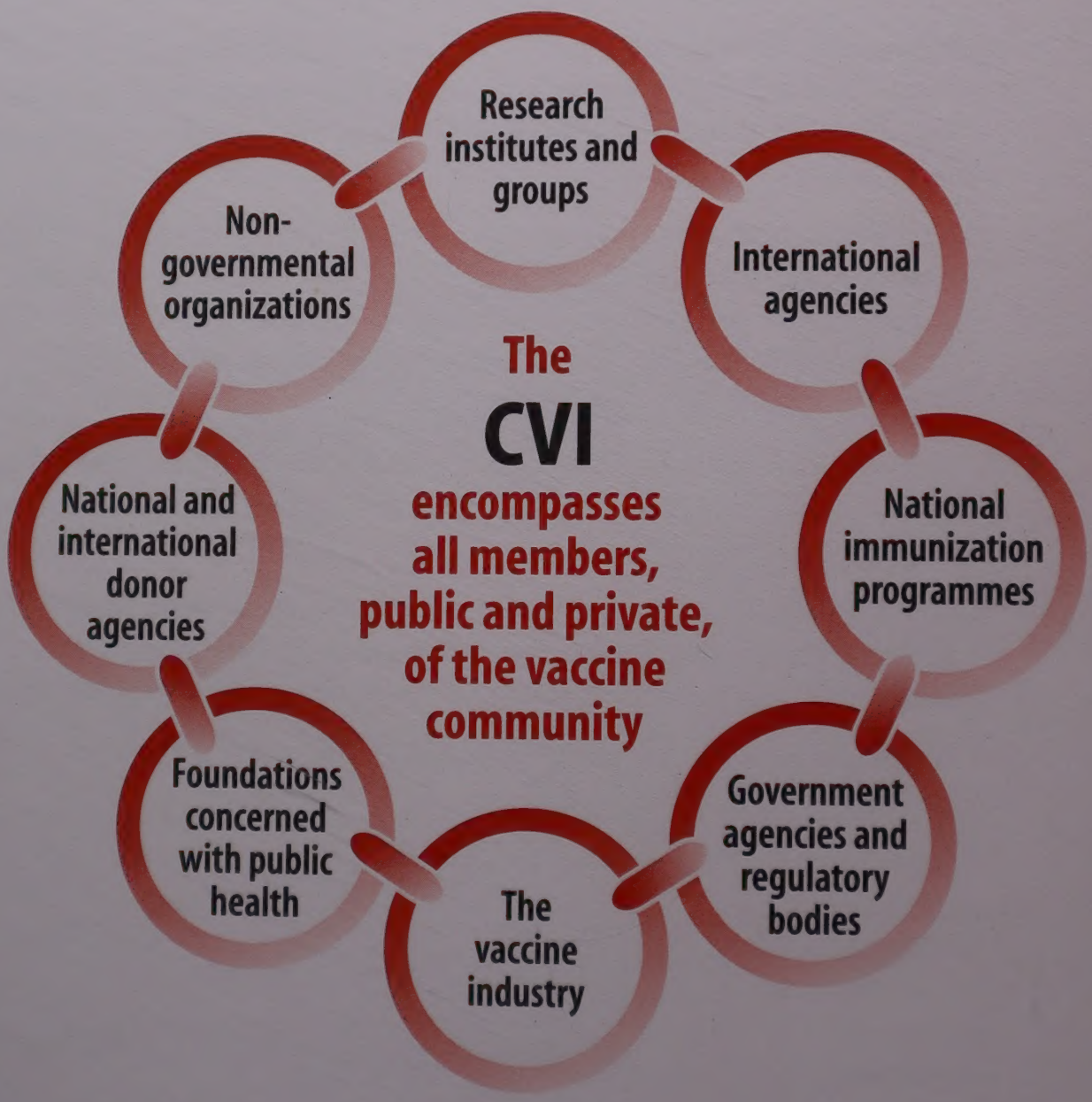
Pros	Cons
• Possibly better disease/epidemiologic data	• Management and legal status could limit production efficiency
• Good response to immunization programme needs, e.g. presentation, price	• Quality may not be assured if public producer exempted from NCA jurisdiction
• Government financing may be more assured	• Price may not cover full cost, or, if they do, may be higher than global market
• Potential for a "captive" market for the producer	• Access to new technologies may be limited

In summary, local vaccine production is often inadequately regulated; inconsistent in quality and quantity; not necessarily cheaper; often subject to fluctuations of political commitment; and unlikely to meet future needs without major attention to access to new, often difficult to master, technologies. Unless this attention is given within a strong management infrastructure which can ensure the sustainability of financial and technical inputs, it will not be a major source of new vaccines for developing countries.

Recommendations

The CVI and WHO recommend the following:

- All countries need appropriate national regulatory systems, depending on their vaccine sources. A fully functioning National Regulatory Authority is essential for a country where vaccines are being produced.
- Governments producing vaccines need to understand clearly the expenditures and needed financing and how to ensure a reliable future supply of vaccines. A viability study performed by a qualified independent management consulting firm is a cost-effective way to accomplish this goal.
- The result of such a viability study should be implemented either by using alternative sources for vaccines or through the execution of a strategic business plan.
- Donors should promote approaches, such as strengthening national regulatory systems and performing viability studies, which will improve the quality and reliability of local production.
- WHO will provide technical support to countries wishing to move forward in any of these activities.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The Children's Vaccine Initiative (CVI)
is a global coalition of organizations from the public, nongovernmental and private sectors, including the vaccine industry, working together to maximize protection against infectious diseases through the development and utilization of safe, effective, easy-to-deliver and widely available vaccines.

Launched at the World Summit for Children in 1990, the CVI is co-sponsored by the United Nations Children's Fund (UNICEF), the United Nations Development Programme (UNDP), the World Health Organization (WHO), the World Bank and the Rockefeller Foundation.

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